THE HILL COEFFICIENT FOR A MONOD–WYMAN–CHANGEUX ALLOSTERIC SYSTEM

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The simple model of Monod, Wyman and Changeux [1] assumes two conformational forms, R and T, of a multi-site enzyme connected together by an isomerization constant, L, which bind statistically substrate, S and positive allosteric effector, A, with intrinsic binding constants K_S and K_A to the R-form, and inhibitor, I, with intrinsic binding constant K_I to the T-form. The degree of saturation with substrate, Y_S, for an n-site enzyme is given [1] by:

$$Y_S = \frac{LK_S[S]\,(1+K_S[S])^{n-1}}{L(1+K_S[S])^n + \left(\frac{1+K_I[I]}{1+K_A[A]}\right)^n} \qquad (1)$$

The slope of the Hill plot [2] for this case is given by:

$$\frac{\delta \ln\{Y_S/(1-Y_S)\}}{\delta \ln[S]} = 1 + (n-1)\,\frac{K_S[S]}{L\left\{(1+K_S[S])\frac{(1+K_A[A])}{(1+K_I[I])}\right\}^n + (1+K_S[S])} \qquad (2)$$

Dahlquist [3,4] has considered the Hill coefficient in general for cooperative systems, but has evaluated it at the half-saturation point in his formulation. If, instead, the Hill coefficient is taken as the maximum value of the slope in eq. (2), then we obtain as the condition for the maximum in the second term at the right of eq. (2):

$$K_S[S](n-1) = 1 + \frac{1}{L\left(\frac{1+K_A[A]}{1+K_I[I]}\right)^n (1+K_S[S_m])^{n-1}} \qquad (3)$$

Here $[S_m]$ represents the substrate concentration at the maximum slope in the Hill plot. When the condition given by eq. (3) is placed in eq. (2), we obtain, after extensive algebraic rearrangement, for the maximum slope, or the Hill coefficient:

$$\text{H.C.} = n\frac{K_S[S_m]}{1+K_S[S_m]} = n(Y_S)_m \qquad (4)$$

The simple relationship of eq. (4) states that the Hill coefficient for the system is just equal to the number of substrate-binding sites per molecule times the degree of saturation at the maximum slope in the Hill plot. Equation (4) is not general, but it holds for the simple Monod–Wyman–Changeux model with or without the presence of allosteric effector and inhibitor.

A test can be made with the carefully obtained, detailed data of Imai [5,6] for the binding of oxygen by normal and abnormal hemoglobins, in the presence and absence of added sodium chloride and organic phosphates. Imai's data show a maximum slope in carefully reconstructed Hill plots which ranges from 1.22–3.11, depending upon the hemoglobin and its environment. For the case of normal adult hemoglobin most completely stripped of organic phosphates, he reports [5] a Hill coefficient of 2.51. Dahlquist [3] has computed a degree of saturation of 0.64–0.65, by recalculating in the form of a Scatchard plot [7] Imai's data [6] for stripped hemoglobin, for which Imai reported a Hill coefficient of 2.78. From eq. (4), the predicted Hill coefficient for this case is simply 4 (0.64–0.65) = 2.56–2.60. From the expression $1/(1-Y_m)$ derived from the position of half-saturation, Dahlquist computes a Hill coefficient

of 2.8–2.9 for this case. At least in principle, it would be possible to compute a Hill coefficient larger than the number of binding sites, at high degrees of saturation, from this formulation. Equation (4) cannot produce a Hill coefficient greater than the number of binding sites, however. When the various Hill plots and their tabulated Hill coefficients given by Imai [6] for hemoglobins are compared with each other, it is also generally observed, as predicted by eq. (4), that higher Hill coefficients occur when the maximum slope is found at a higher degree of saturation. This appears to hold when comparing normal with abnormal hemoglobin, as well as when comparing the effects of adding organic phosphates to these systems. Thus, again, eq. (4) appears to be verified.

This simple result in eq. (4) should serve as a quick method for correlating Hill coefficients for cooperative systems with their degree of saturation, and as one test of the applicability of the simplest form of the Monod–Wyman–Changeux model to specific cooperative systems.

References

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